

203. A method according to claim 189, further comprising a step of manufacturing a medicament for the treatment of Alzheimer's Disease with an inhibitor identified according to steps (a)-(c).

204. A method for assaying for modulators of β -secretase activity, comprising the steps of:

(a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a polypeptide according to claim 151, and wherein the second composition comprises a substrate polypeptide having an amino acid sequence comprising a β -secretase cleavage site;

(b) measuring cleavage of the substrate polypeptide in the presence and in the absence of the putative modulator compound; and

(c) identifying modulators of β -secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β -secretase antagonist reduces such cleavage and a modulator that is a β -secretase agonist increases such cleavage.

205. A method according to claim 204, wherein the polypeptide of the first composition comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

206. A method according to claim 204, wherein the polypeptide of the first composition is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, and wherein the measuring step comprises measuring APP processing activity of the cell.

207. A method according to claim 204, wherein the first composition comprises a purified human Asp2 polypeptide.

208. A method according to claim 204, wherein the first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 β -secretase activity.

209. A method according to claim 208 wherein the soluble fragment is a fragment lacking an Asp2 transmembrane domain.

210. A method according to claim 208, wherein the substrate polypeptide of the second composition comprises the amino acid sequence SEVNLDAEFR.

211. A method according to claim 208, wherein the substrate polypeptide of the second composition comprises the amino acid sequence EVKMDAEF.

212. A method according to claim 208, wherein the second composition comprises a polypeptide having an amino acid sequence of a human amyloid precursor protein (APP).

213. A method according to claim 212, wherein the human amyloid precursor protein is selected from the group consisting of: APP695, APP751, and APP770.

214. A method according to claim 213, wherein the human amyloid precursor protein includes at least one mutation selected from a KM→NL Swiss mutation and a V→F London mutation.

215. A method according to claim 212, wherein the polypeptide having an amino acid sequence of a human APP further comprises an amino acid sequence comprising a marker sequence attached amino-terminal to the amino acid sequence of the human amyloid precursor protein.

216. A method according to claim 212, wherein the polypeptide having an amino acid sequence of a human APP further comprises two lysine residues attached to the carboxyl terminus of the amino acid sequence of the human APP.

217. A method according to claim 204, wherein the second composition comprises a eukaryotic cell that expresses amyloid precursor protein (APP) or a fragment thereof containing a β -secretase cleavage site.

218. A method according to claim 217, wherein the APP expressed by the host cell is an APP variant that includes two carboxyl-terminal lysine residues.

219. A method according to claim 204, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

220. A method according to claim 204, further comprising a step of manufacturing a medicament for the treatment of Alzheimer's Disease with a modulator identified as an antagonist according to steps (a)-(c).

221. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

- (a) growing a cell in the presence and absence of a test agent, wherein the cell expresses a polypeptide according to claim 151 and expresses an amyloid precursor protein (APP) that comprises a carboxy-terminal di-lysine (KK);
- (b) determining the APP processing activity of the cell in the presence and absence of the test agent; and
- (c) comparing the APP processing activity in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

222. A method according to claim 221, wherein the APP further comprises the Swedish mutation (K \rightarrow N, M \rightarrow L) adjacent to the β -secretase processing site.